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A study on ECG and cardiac functional changes in patients with B-thalassemia major

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Abstract

Background
Cardiovascular complications such as heart failure and arrhythmias caused by 'iron-overload' cardiomyopathy are a leading cause of death in patients with thalassemia major (TM).

Aims
The study aims to determine the prevalence of cardiac complications in patients with B-TM. This will include cardiac function and electrocardiologic changes, as well as an examination of the relationship between these cardiac complications and various factors, including iron overload, in a 5-year cross-sectional study.

Patients and methods
After approval by the General Organization of Teaching Hospitals and Institutes' Ethics Review Committee, 40 patients with B-TM and 20 normal children meeting the inclusion criteria were recruited from Ahmed Maher Teaching Hospital. All patients underwent thorough clinical examination, laboratory tests, ECG, and two-dimensional echocardiography with spectral and color flow Doppler analysis.

Results
All ECG parameters increased in patients compared with the control group ($P = 0.05$), most notably PR interval $r = 0.336$, 95% confidence interval 0.01–0.625, $P = 0.032$. Echocardiography findings revealed that the posterior wall thickness of the left ventricle, the thickness of the intraventricular septum, mass of the left ventricle, and the mass index of the left ventricle were significantly greater in the patient group with elevated ferritin levels ($P = 0.05$).

Conclusion
Cardiac function, arrhythmia screening, and ferritin levels should be evaluated on a regular basis in patients with TM to detect early signs of cardiac complications.

Keywords: Cardiac functions, ferritin levels, iron overload, thalassemia

Introduction

Thalassemia major (TM) is an inherited chronic hemolytic anemia caused by a reduced synthesis rate of the beta goblin chain. This condition shows more prevalence in the so-called (thalassemia belt) including the Mediterranean Region, the Middle East, and some parts of Asia [1]. TM patients require regular blood transfusions for survival. Increased intestinal iron absorption finally leads to iron accumulation in the reticuloendothelial cells and in the parenchymal tissues [2]. Iron overload and free iron causes the Fenton-type reaction and hemochromatosis [3]. Myocardial siderosis is one of the important causes of mortality in

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patients with TM patients [4]. Congestive heart failure (CHF), arrhythmias, and sudden deaths continue to occur. Strikingly, this also occurs even with a good chelation therapy [4]. Hence, regular evaluation of cardiac function is recommended [5].

However, the exact role of echocardiography monitoring in the long-term management of TM is yet to be cleared and screening of cardiac function should identify at-risk patients before the development of CHF. The mortality rate of iron overload-related cardiomyopathy is still high because of late detection, and this can be prevented by starting effective chelation [6,7].

ECG and arrhythmic abnormalities are found in TM patients, especially with inadequate chelation and in the presence of CHF [8]. ECG changes can occur in TM patients before the occurrence of TM-related cardiomyopathy. These include T-wave and ST interval changes, prolonged QT interval, and conduction defects [9]. Arrhythmias encountered usually include atrial fibrillation, atrial flutter, and atrial tachycardia. Ventricular arrhythmias are more familiar with severe iron cardiac load [10]. This study evaluated the prevalence of cardiac complications in patients with B-TM, including cardiac function and electrocardiologic changes. Also, the relation between these cardiac complications and different factors is studied, including iron overload, in a cross-sectional study over a period of 5 years.

Patients and Methods

A cross-sectional study was conducted on 40 patients with B-TM and 20 normal children after approval by the Ethics Committee of the General Organization of Teaching Hospitals and Institutes. Patients fulfilling the inclusion criteria were recruited from Ahmed Maher Teaching Hospital over 5 years. Patients were informed of the nature of the study and its aims were all explained. Consent was taken from the patients or their caregivers. The control group included 20 normal children in the same age group.

Inclusion criteria

(1) Age: 18 years and below.
(2) Sex: both males and females.
(3) Attending pediatrics and hematology departments in the hospital for 5 years.
(4) Clinical and laboratory diagnoses of B-TM (Ambrosino *et al.*, 1959).
(5) Patients on blood transfusion and chelation therapy are defined as at least eight transfusions per year. All patients were on variable levels of chelation therapy.
(6) Acceptance to participate in the study.

Exclusion criteria

(1) Congenital or rheumatic heart disease.
(2) Other chronic diseases.
(3) Refusal to cooperate.
(4) Failure to obtain consent.

Methods

All patients were subjected to the following:

(1) Accurate history taking included reviewing patients' records for duration and course of the disease, age of beginning of treatment, treatment regimen, associated infections or complications, splenectomy status, family history of siblings or relatives with thalassemia and any deaths among them.
(2) Thorough clinical examination:
   (a) General and systemic examination, including growth, chest, and abdomen.
   (b) Thorough local cardiac examination.
(3) Laboratory investigations:
   (a) Complete blood count and reticulocyte count.
   (b) Serum ferritin and serum iron.
(4) ECG:
   The ECG was recorded using a conventional 12-lead ECG (Fukuda Denshi Fx-2111) at a paper speed of 25 mm/s and then analyzed for changes by a consultant cardiologist who was blinded to the patient's clinical status. Sinus bradycardia was defined as a resting heart rate of less than 60 beats per minute, while sinus tachycardia was defined as a resting heart rate of more than 100 beats per minute [11]. We plotted the Children under the age of 10 years on a centile chart according to their age [12] and [13]. The length of the rhythm QT interval (time of electrical systole) is determined using a stable isoelectric line. If a U-wave exists, the QT interval is determined by the nadir of the curve connecting the T and U waves.
   QT interval is corrected (QTc) with Bazzet's formula [14]:
   QTc = measured QT interval in fractions of a second/V (R-R) interval in fractions of a second.
   Prolonged if more than 440 ms in children less than 10 years and more than 430 ms more than 10 years [15].
   (a) PR intervals: considered first-block if more than or equal to 200 ms.
   (b) QRS interval:
      Considered complete intraventricular conduction delay if more than or equal to 120 ms.
      Incomplete intraventricular conduction delay if 100–119 ms [11].
(5) Echocardiography [11]:

M-mode and two-dimensional echocardiography with spectral and color flow Doppler analysis are performed on patients using a Philips HD 11 XE ultrasound machine equipped with a 2 0.40 MHz transducer. All conventional views are used during the examination, which is performed in left lateral decubitus.

The following parameters are considered:

Heart rate, cardiac output, pulmonary artery pressure, left ventricular end-diastolic and end-systolic diameters, right ventricular end-diastolic and end-systolic diameters. In addition, the thickness of the interventricular septal wall and posterior left ventricular wall (PWT) (mm). Systolic function is determined by the left ventricle's ejection fraction (EF), which is expressed as a percentage and calculated using the area–length method.

The E/A ratio is used to determine diastolic function (E velocity = early maximal ventricular filling velocity). By analyzing trans-mitral flow, we can determine the A velocity (late diastolic or atrial velocity) and the deceleration time (time from peak E-wave to baseline).

Feigenbaum *et al*. [16], reported that normal echocardiographic values are used as references. After the collection of data, the data analysis is performed, and the two groups will be compared for ECG and functional abnormalities in:

Patients with Thalassemia Major, normal candidates and the effect of iron overload.

Statistical analysis

SPSS software was used to conduct the statistical analysis (version 25.0; SPSS Inc., Chicago, Illinois, USA). If the continuous variable distributions were normal, they were expressed as mean SD ($P > 0.05$ on the Kolmogorov–Smirnov or Shapiro–Wilk tests; $n = 30$). If continuous variables were not normally distributed, the median was used to describe them (minimum–maximum). For normally distributed data, Student's *t* test or one-way analysis of variance was used; for nonnormally distributed data, the Mann–Whitney *U* test or Kruskal–Wallis test was used. Correlations between variables were determined using the Spearman correlation coefficient, and *P* values less than 0.05 were considered statistically significant.

Results

Forty patients were studied, 60.98% females and 39.02% males with an age average of 12 ± 6 (6–18) years. The control group consisted of 20 individuals, including 12 (60%) females and eight (40%) males with an age average of 11 ± 7 (4–18) years. No statistical significance was detected between the patient and control groups for age and sex ($P = 0.434$ and 0.806, respectively). Weight, height, and BMI all decreased significantly in the patient group compared with the control group ($P = 0.001$, 0.001, and 0.027, respectively). Hemoglobin levels were lower in the patient group. Platelet count, total bilirubin, and ferritin levels, on the other hand, were significantly higher than those in the control group ($P = 0.001$, 0.001, and 0.008, respectively).

The ECG and ECHO results are shown in Table 1. The ECG parameters (heart rate, P-wave dispersion, P-wave duration, PR interval, QRS complex duration, QT-wave dispersion, QTc duration, QTc dispersion, JT duration, JTc duration, JTc dispersion, T peak-end, T peak-end dispersion, and T peak-end/QT ratios) were all significantly higher in the patient group than in the control group ($P = 0.05$). As for echocardiography findings, EF was less than 55% in one patient only, while normal in other patients. The IVST was more than 10 mm – higher than normal – in two patients, while normal in all others. Shortening fraction (FS) and LVPWT were in the normal range in all. Moreover, LVEDD and LVESD were in the normal ranges in all patients. No statistical significance was seen comparing the ECHO parameters with the control group (P = ns). However, LVM and LVMI were higher among the patients in comparison to the controls and statistically significant ($P = 0.004$ and 0.009, respectively).

Table 1: ECG and ECHO results

Parameters	Patient group ($n=40$) (mean±SD)	Control group ($n=20$) (mean±SD)	*P*
ECG			
HR (bpm/min)	74±12	71±6	0.043
P-wave duration (ms)	97±9	91±3	0.002
P-wave dispersion (ms)	60±10	52±20	0.003
PR interval (ms)	142±10	128±10	0.001
QRS complex duration (ms)	90±10	82±6	0.001
QT-wave duration (ms)	389±32	355±26	0.001
QT dispersion (ms)	29±10	12±9	0.001
QTc duration (ms)	420±16	408±12	0.001
QTc dispersion (ms)	28±9	12±10	0.001
JT duration (ms)	305±36	274±20	0.014
JTc duration (ms)	319±39	276±42	0.001
JTc dispersion (ms)	73±29	39±12	0.001
Tp-e interval (ms)	97±19	82±10	0.001
Tp-e dispersion (ms)	69±11	48±19	0.005
Tp-e/QT	0.25±0.05	0.23±0.03	0.045
ECHO			
EF (%)	62±4	64±3	0.734
FS (%)	41±4	38±5	0.645
LVEDD (mm)	46±4	42±3	0.270
LVESD (mm)	30±3	27±4	0.338
IVST (mm)	10±2	8±1	0.052
LVPWT (mm)	9±1	8.8±1	0.294
LVM (g)	142±30	121±16.75	0.004
LVMI (g/m^2)	75±10	70±8	0.009

Student's *t* test, *P* value less than 0.05. ECHO, echocardiography; EF, ejection fraction; FS, shortening fraction; HR, heart rate; IVST, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass, LVMI left ventricular mass index; LVPWT, left ventricular posterior wall thickness; Tp-e, T peak-to-end

In the patient group, we examined the relationship between ECG and ECHO findings and ferritin levels. The heart rate and PR interval were found to be positively correlated with ferritin when the association between ECG and ECHO findings and ferritin in the patient group was considered. Other ECG and ECHO findings had no correlation with ferritin (Table 2).

Discussion

The association between ECG, ECHO, and ferritin levels in patients with TM revealed that ECG parameters were significantly increased in the patient group when compared with the control group. In addition, LVM and LVMI levels were significantly increased in the patients. With regard to the ECG and ECHO, the results indicated a positive correlation between ferritin and HR and PR intervals.

Table 2: Correlation with Serum Ferritin

Parameters	Ferritin		
	r	95% CI	*P*
HR	0.3	(−0.023)-(0.588)	0.04
Duration of P-wave	0.09	(−0.252)-(0.393)	0.58
PR interval	0.3	(−0.01)-(0.625)	0.03
QT-wave duration	−0.05	(−0.401)-(0.290)	0.7
QT dispersion	0.18	(−0.151)-(0.489)	0.26
QRS-C duration	0.16	(−0.181)-(0.458)	0.33
QTc duration	0.13	(0.231)-(0.465)	0.42
QTc dispersion	0.17	(−0.149)-(0.466)	0.29
JT duration	0.02	(−0.272)-(0.316)	0.9
JTc duration	0.2	(−0.108)-(0.487)	0.2
EF (%)	0.17	(0.004)-(0.287)	0.3
Tp-e	0.14	(−0.192)-(0.415)	0.4
Tp-e/QT	0.17	(−0.136)-(0.456)	0.3
LVEDD	−0.06	(−0.246)-(0.224)	0.7
LVESD	−0.2	(0.203)-(0.254)	0.3
IVST	0.09	(−0.298)-(0.365)	0.6
LVMI	0.1	(−0.204)-(0.389)	0.5
LVPWT	0.2	(−0.319)-(0.441)	0.3
LVM	0.3	(−0.093)-(0.533)	0.1

r, correlation coefficient. CI, confidence intervals; EF, ejection fraction; HR, heart rate; IVST, intraventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; QRS-C, QRS complex duration; Tpe T, peak-to-end interval

In our study, patients with TM had lower height, weight, and BMI values than the control group. In addition, the hemoglobin level was decreased and the platelet count was increased. As expected, the patient group had elevated total bilirubin and ferritin levels due to hemolysis and frequent transfusions. Inadequate growth can be attributed to anemia, which, in combination with inadequate compliance with iron chelation therapy, results in impaired growth hormone production [17].

Pericarditis, arrhythmias, and myocardial dysfunction are all possible complications of iron overload in B-TM, with an increased prevalence of atrial fibrillation. This may be explained by structural and electrical remodeling of the atrium, as well as autonomic disturbances [18]. Increased P-wave duration and distribution are indicative of atrial electrical and structural changes. In addition, it seems as though iron deposition plays a critical role in atrial structural and electrophysiological remodeling, thereby promoting atrial fibrillation. All ECG results were significantly prolonged in patients compared with controls. The PR interval is one of the ECG symptoms of cardiac failure. An abnormal T-wave is a late finding that is more prevalent in individuals who are older and have a higher iron load [19]. After the first decade, atrial extrasystoles may occur, while ventricular extrasystoles may occur in the middle of the second decade [20]. In previous studies examining iron overload in cardiac conduction systems, paroxysmal atrial tachycardia, flutter, and fibrillation were also observed [21].

ECHO was used to determine the EF, FS, LVEDD, LVESD, IVST, and LVPWT. The LVM and LVMI were significantly higher in patients than in controls, but no other ECHO parameters were significantly different. Although the increase in IVST was not statistically significant, it was observed in the patients. Cardiac iron overload manifests as hypertrophy and fibrosis of the myocardium. Cardiovascular decompensation due to myocardial iron overload typically occurs between the ages of 20 and 30 years. Heart failure is responsible for 70% of deaths, according to studies [6,22,23]. Iron deposits in cardiac muscle myocytes and the free iron atoms increase the free radicals, causing impairment of the mitochondrial respiratory chain [24].

Limitations

Limitations of this study included limitations in the number of patients, and this was compensated by a more extended period for the conduction of the study. Other constraints were the cost of ECHO and ECG supplies and the cost of kits and parental refusal for sharing in the study.

Conclusion

Our study demonstrated that B-TM has an effect on the cardiac electric depolarization and repolarization parameters. In addition, we discovered that changes were more pronounced in patients with a higher cardiac iron load. Thus, we concluded that the ferritin, ECG, and ECG should all be carefully evaluated to gain a better understanding of the prognosis of patients with B-TM.

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Conflicts of interest

None declared.

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